Medulloblastoma: From Myth to Molecular
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ABSTRACT

Current therapies for medulloblastoma were introduced primarily in the 1980s and consist of predominantly cytotoxic, nontargeted approaches. Mortality from medulloblastoma remains significant. In addition, many survivors suffer from severe treatment-related effects of radiation and cytotoxic chemotherapy. Further intensification of nonspecific therapy is unlikely to offer additional benefits, because survival rates have reached a plateau. Recent publications in medulloblastoma have revolved largely around the recognition that medulloblastoma per se does not exist, but rather, that there are a group of histologically similar but clinically and molecularly distinct entities that have been grouped under that rubric. Distinguishing the four molecular subgroups of medulloblastoma—wingless (WNT), sonic hedgehog (SHH), group 3, and group 4—in the daily treatment of patients, as well in the setting of clinical trials, is an important challenge in the near term for the pediatric neuro-oncology community. The preponderance of morbidity in treating patients with medulloblastoma is secondary to the treatment or prophylaxis of leptomeningeal metastases, and the cause of most deaths is leptomeningeal metastases. Recurrence of medulloblastoma is a nearly universally fatal event, with no significant salvage rate. The extent of spatial and temporal intratumoral heterogeneity as medulloblastoma metastasizes to leptomeninges and as it evolves in the face of radiation and cytotoxic chemotherapy is just beginning to be understood as a major barrier to therapeutic success. Pediatric neuro-oncology clinicians and scientists must now determine how best to incorporate rapid changes in our biologic understanding of medulloblastoma into the next generation of upfront clinical trials, with the goal of both improving survival for the highest-risk patients and improving quality of life for survivors.

INTRODUCTION

Medulloblastoma, the most common malignant brain tumor of childhood, was described initially by Cushing and Bailey in the 1920s as a small blue cell tumor of the cerebellum.1 During the latter years of the 20th century, medulloblastoma and intracranial primitive neuroectodermal tumors were considered similar entities because of their comparable morphology. This controversy in nosology extended to the WHO classification and clinical trial stratification.2,3 Moreover, before the clear identification of atypical teratoid/rhabdoid tumors (ATRTs) as a distinct entity, with loss of SMARCB1–INI1, cerebellar ATRTs were commonly classified as medulloblastoma.4,5 Molecular profiling subsequently confirmed the original description that medulloblastoma comprises a distinct entity, separate from other intracranial embryonal tumors.6,7 The revised 2016 WHO classification of CNS tumors defines medulloblastoma both histologically and genetically.8 The histologic classification consists of desmoplastic-nodular, classic, large-cell–anaplastic, and medulloblasto ma with extensive nodularity (MBEN). Most medulloblastosmas have classic histology. MBENs are restricted to infants, but desmoplastic-nodular–enriched medulloblastoma may occur in infants and adults.8-10 The WHO genetic classification divides tumors into wingless (WNT)-activated, sonic hedgehog (SHH)-activated–TP53 wildtype, SHH-activated–TP53 mutant, and non–WNT-SHH, where group 3 and group 4 medulloblastosmas are included as provisional entities when a diagnosis is possible. There is overlap between the histologic and genetic classifications; desmoplastic-nodular and MBEN tumors are almost exclusively SHH-activated tumors, and large-cell–anaplastic tumors are enriched for SHH-TP53–mutant, or high-risk group 3 tumors. The usefulness of identifying large-cell–anaplastic morphology in WNT and group 4 is unclear.11 Overall, genetic classification has been
shown to be more reliable and robust, and it forms the basis for the next generation of clinical trials.\textsuperscript{10,11}

**Current Risk Stratification and Treatment**

Currently, medulloblastomas in children older than 3 to 5 years are stratified into average (or standard-risk in Europe) and high-risk groups. High-risk disease is defined by residual disease \( > 1.5 \text{ cm}^2 \), metastatic dissemination, and, in some studies, large-cell–anaplastic histology.\textsuperscript{12} Infants under the age of 3 to 5 years are treated with radiation-sparing protocols. Adults have been a historically neglected group and are treated mostly with radiation-only approaches.\textsuperscript{13}

The origins of current therapy are complex and date back to the 1920s, when Cushing and Bailey observed that in the setting of complete surgical resection, relapse was inevitable.\textsuperscript{14} By 1953, 3-year survival had reached 50% when patients were treated with craniospinal irradiation of at least 30 Gy with the posterior fossa boosted to 50 Gy.\textsuperscript{15} By 1969, metastatic dissemination as defined by Chang staging (M0 to M4) could significantly predict poor outcome.\textsuperscript{16}

Medulloblastoma metastasizes largely to the pial surface of the spinal cord and brain in the so-called leptomeninges. The need to provide prophylaxis against future leptomeningeal relapse or the treatment of frank magnetic resonance imaging–visible metastases is the justification for irradiation of the entire nervous system and not just the primary tumor bed. This irradiation of the entire CNS is the major source of severe neurocognitive morbidity in long-term medulloblastoma survivors. This prompted trials evaluating adjuvant chemotherapy, reductions in craniospinal irradiation for average-risk patients, and the elimination of radiation in infants under the age of 3 to 5 years (age cutoffs vary by cooperative group). Although residual disease was never evaluated formally, studies from the 1980s suggested that it was a marker of poorer outcome, when 1.5 \text{ cm}^2 \text{ was the limit of detection on postoperative computerized tomography.}\textsuperscript{12}

Currently, high-risk patients older than 3 to 5 years are treated with craniospinal irradiation of 36 to 39 Gy, with a boost to 55 Gy to the posterior fossa–tumor bed, followed by cisplatin–cyclophosphamide–based chemotherapy. This results in 5-year survivals of 60% to 65% across most studies\textsuperscript{17-22} Average-risk patients receive 23.4 Gy of craniospinal irradiation, with a boost to 55 Gy to the posterior fossa–tumor bed, followed by adjuvant chemotherapy. Average-risk patients achieve 5-year outcomes of approximately 80%, independent of the regimen used.\textsuperscript{23,24} Patients with residual disease have a more favorable outcome compared with those with metastatic disease. It is clear that unselected patients with metastatic disease treated with 23.4 Gy have a dismal outcome.\textsuperscript{24}

Infants are treated with radiation-sparing approaches because of the devastating long-term sequelae of radiation to the entire neuroaxis. Early studies focused on delaying radiation therapy until the age of 3 years, whereas subsequent studies of more intensive chemotherapy revealed that some nonmetastatic infants could be cured without radiation.\textsuperscript{25-30} Importantly, radiation avoidance in infants results in superior neurocognitive outcomes.\textsuperscript{31} Infants with nondesmoplastic metastatic disease (specifically group 3) continue to have dismal outcomes without radiation therapy.

Current risk stratification and therapies applied since the late 1980s pose tremendous challenges. Survival has been stagnant for almost 30 years despite the intensification of therapy.\textsuperscript{32} Moreover, incremental advances in anesthesia, radiation, neurosurgery, and diagnostic imaging over the past three to four decades have affected patient outcomes as much as the actual treatments administered. Practices such as increased craniospinal dose in the setting of residual disease and anaplastic morphology are based on the exclusion of presumed high-risk groups from average-risk studies, rather than on an evidence-based rationale that an increased craniospinal dose improves outcome.\textsuperscript{11,33}

**Molecular Classification of Medulloblastoma**

Initial attempts to molecularly classify medulloblastoma using transcriptomics demonstrate that medulloblastomas cluster apart from ATRTs and primitive neuroectodermal tumors and that combining transcriptomics with clinical parameters stratifies patients more robustly than do clinical criteria alone.\textsuperscript{6,34} A group of favorable-risk patients expressing nuclear \(\beta\)-catenin (WNT subgroup) was identified as having survivals of close to 100%.\textsuperscript{17,35}

Transcriptional profiling of larger cohorts consistently identified four distinct molecular entities termed WNT, SHH, group 3, and group 4.\textsuperscript{36-41} These four subgroups likely arise from distinct cells of origin, and, unlike that of glioblastoma, medulloblastoma subgroup affiliation is stable at recurrence.\textsuperscript{42-44} The four subgroups have distinct clinical and molecular characteristics and form the basis of future preclinical modeling and clinical trial design (Fig 1).\textsuperscript{10,42,43,45-57}

**WNT-ACTIVATED MEDULLOBLASTOMA**

WNT tumors have activated WNT signaling. They rarely metastasize, have a longer prediagnostic interval, occur in older patients, and have a balanced sex ratio.\textsuperscript{40,41,53,58} WNT tumors frequently invade the lateral recess of the brainstem, probably because their cell of origin resides in the lower rhombic lip.\textsuperscript{42,54}

Highly recurrent, activating somatic mutations in exon 3 of \(\beta\)-catenin (\textit{CTNNB1}) are found in 85% to 90% of WNT tumors, whereas monosomy 6 is seen in 70% to 80%,\textsuperscript{9,41,47} Less frequent events include somatic mutations in \textit{TP53}, \textit{SMARCA4}, and \textit{DDXX}.\textsuperscript{46-48,52,59} Unlike \textit{TP53} mutation in SHH tumors, \textit{TP53} mutation in WNT tumors is not prognostic.\textsuperscript{59} Rare germline mutations in \textit{APC}, consistent with Turcot syndrome, have been reported in WNT tumors lacking \textit{CTNNB1} mutations, and emerging data suggest referral for genetic counseling in such cases.\textsuperscript{60}

Patients younger than 16 years with WNT tumors have a favorable outcome across multiple studies and consistently show 5-year survival rates of \(>95\).\textsuperscript{10,11,56,57,61} Patients older than 16 years with WNT tumors have indeterminate outcomes.\textsuperscript{39,61,62} As such, rationale therapies for patients with WNT tumors involve de-escalation of therapy in current clinical trials (\textit{ClinicalTrials.gov} identifiers: NCT02066220, NCT01878617, and NCT02724579).

**SHH-ACTIVATED MEDULLOBLASTOMA**

SHH tumors are characterized transcriptionally and genetically by activation of the SHH pathway.\textsuperscript{36,37,40,41,58,63} Infrequently
metastatic at diagnosis, these tumors have a short presymptomatic interval and occur across all ages. SHH tumors are almost exclusively located within the cerebellum rather than in the fourth ventricle, consistent with their cells of origin (granule cell progenitors).42,53-55 Children between the ages of 3 and 16 years have a metastatic at diagnosis, have short prediagnostic intervals, and are frequently germline.34,35 Group 3 tumors occur in younger children, 40% to 50% are somatic,10,59,63 The majority of transgenic preclinical mouse models of medulloblastoma are SHH tumors, including a metastatic model.66,69

Outcomes of SHH tumors are age specific. Infants have an excellent outcome, even with chemotherapy-only regimens.9,70 In childhood, TP53-mutant SHH tumors have a dismal prognosis compared with that of TP53-wildtype tumors.10,59 SHH pathway antagonists such as SMO inhibitors are currently being evaluated in clinical trials; however, concerns exist regarding premature osseous fusion. Additionally, high-risk SHH patients are unlikely to benefit from their use because of activation of the SHH pathway downstream of SMO, limiting widespread clinical adoption.63,71 New preclinical therapeutic avenues for the highest-risk group of SHH patients focus on agents acting on downstream targets of the SHH pathway, such as bromodomain inhibitors, PI3K inhibitors, aurora kinase inhibitors, iraconazole, arsenic trioxide, and GLI antagonists.72-75

GROUP 3 MEDULLOBLASTOMA

Group 3 tumors are characterized transcriptionally by the activation of the GABAergic and photoreceptor pathways.37,40,41,58 Group 3 tumors occur in younger children, 40% to 50% are metastatic at diagnosis, have short prediagnostic intervals, and a male preponderance.53,58 Anatomically, they are located in the fourth ventricle up against the brainstem. Metastatic group 3 tumors frequently have small primaries.55

Somatic nucleotide variants, which have been considered copy number–driven tumors because of the frequency of structural genomic variations, are rare in group 3.46-49,52 The most common cytogenetic aberration is amplification of MYC, (10% to 20% of tumors), which occurs frequently as a fusion with PVT1 secondary to complex chromosomal rearrangements at the 8q24
GROUP 4 MEDULLOBLASTOMA

Group 4 tumors are characterized transcriptionally by over-representation of neuronal and glutaminergic pathways. Group 4 tumors are the predominant subgroup in children 3 to 16 years of age and have long prediagnostic intervals, and 30% and 40% are metastatic at diagnosis. They often present with a nonenhancing primary on initial magnetic resonance imaging. Somatic nucleotide variants are rare, and group 4 medulloblastomas are also considered copy number–driven tumors. The most common are inactivating mutations of the histone demethylase KDM6A, which occur in 10% of cases. Tandem duplications of SNCAIP are identified in 10% of tumors and are mutually exclusive of amplifications of CDK6 and MYCN, which are observed in 5% to 10% of tumors. Unlike SHH tumors, MYCN amplifications do not confer a poor prognosis in group 4 medulloblastomas. The most common cytogenetic aberration is i17q, seen in almost 80% of tumors, with less frequent aberrations in 8p, 7q, 11p, and 18q. No known preclinical models exist for MYC-amplified group 3 tumors. Patients with group 3 tumors have a poor outcome overall, particularly nonirradiated infants, but likely benefit from myeloablative treatment regimens. Although patients with radiated nonmetastatic group 3 tumors have intermediate outcomes, patients with metastatic group 3 tumors have a poor outcome. Metastases and/or MYC amplification confer a poor prognosis for patients with group 3 tumors; however, the significance of MYC amplification in nonmetastatic group 3 tumors is indeterminate. i17q is also a possible marker of poor prognosis in group 3 tumors.

RECURRENT MEDULLOBLASTOMA

Salvage rates for recurrent medulloblastoma are < 10% in previously irradiated children. Unsuccessful approaches tested previously include repeat surgery, re-irradiation, and multiple chemotherapy regimens including myeloablative chemotherapy. In rare instances, infants treated previously with only chemotheraphy can be salvaged with 36 Gy of craniospinal irradiation at relapse, albeit with profound neurocognitive sequelae. The temporal and spatial pattern of relapse is highly subgroup dependent. Group 4 tumors recur later than either SHH or group 3 tumors and survive significantly longer postrecurrence. Independent of treatment, the anatomic location of relapse is subgroup dependent; SHH tumors recur predominantly locally; group 3 and 4 tumors recur almost exclusively with metastatic.

Unanswered Controversies

Despite the agreement that medulloblastoma comprises four distinct molecular subgroups, it was acknowledged as early as in the original consensus that additional heterogeneity exists, specifically subtypes of group 4. Specifially, there exists age-dependent heterogeneity in SHH, MYC–activated groups in group 3, and copy number–driven group 4 groups; however, the true extent of intrasubgroup heterogeneity is unknown.

A second issue that still requires clarification is the boundary between groups 3 and 4. The WHO classification includes them as provisional entities under the umbrellas of non-WNT and non-SHH. Groups 3 and 4 share several copy number aberrations such as enrichment of i17q and the fact that they consistently cluster closer to one another than do WNT or SHH. The degree and nature of the overlap between groups 3 and 4 is an active area of exploration and continued investigation that must be resolved to accurately stratify patients in future molecularly informed clinical trials.

Subgroup Ascertainment

There are several current methods of subgroup determination, including immunohistochemistry, gene expression profiling, and genome-wide methylation profiling. Immunohistochemistry is the least robust of these methods and can identify patients with WNT using a nuclear localization of β-catenin and patients with SHH using GAB1 immunoreactivity. At least two methods of subgrouping should be used, particularly when changes in clinical management are involved, because some non-WNT tumors have nuclear localization of β-catenin. To robustly identify all four subgroups, including groups 3 and 4, either gene expression or DNA methylation profiling is required.

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dissemination, usually without any evidence of disease in the previously treated surgical bed.\textsuperscript{43} Although rare, WNT tumors can recur in either the tumor bed or with metastatic dissemination.\textsuperscript{43,94} Isolated metastatic relapses are more common in group 4, whereas diffuse relapses are more common in group 3.

A major barrier to the treatment of recurrent medulloblastoma is temporal heterogeneity. Although subgroup affiliation on the basis of transcription or DNA methylation patterns remains stable, likely related to a conserved cell of origin, most somatic nucleotide variants and copy number events are not conserved between diagnosis and relapse.\textsuperscript{43,81,95} Evaluation of paired samples from diagnosis and relapse revealed drastic genetic divergence after therapy, with only a fraction of events shared between both samples, including the emergence of TP53 mutations and MYC amplifications at recurrence.\textsuperscript{81,95} This suggests that treatment results in a clonal squeeze caused by expansion of a treatment-resistant clone (Fig 2). Patients with group 3 or 4 medulloblastoma die almost exclusively as a result of metastatic disease, which suggests that a treatment-resistant clone in the metastatic compartment results in relapse.\textsuperscript{43} These observations are consistent with a cross-species analysis of metastatic medulloblastoma where metastatic clones are an early event and are genetically divergent from the primary tumor (Fig 3).\textsuperscript{69} This represents a tremendous treatment challenge in the context of personalized therapies and suggests that concurrent biopsy is warranted if targeted agents are to be used at recurrence, both to confirm the presence of the target and to exclude secondary radiation–induced glioblastoma, particularly in late relapses.\textsuperscript{11,42}

\textbf{Fig 2.} Resistance to treatment in recurrent group 3 and 4 medulloblastoma. Circles represent individual clones. The clones populating the metastatic compartment at recurrence are highly disparate from the primary site and are more similar to each other. Note the absence of tumor in the primary site after radiation therapy.

\textbf{Fig 3.} Clonal selection drives seeding of the metastatic compartment in medulloblastoma. Proposed progression of metastatic dissemination with tumor initiation from the cell of origin, followed by expansion of clones within the tumor. Metastatic clones are shed out of the primary site, and surviving clones then reseed along the leptomeningeal space, followed by growth of highly divergent clones in the leptomeningeal compartment. Metastatic clones are disparate from the primary tumor and are more similar to each other than to the primary.
Major barriers to the treatment of recurrent medulloblastoma include a lack of bona fide model systems and the continued practice in the field of studying the primary tumor, rather than searching for treatments specific to the metastatic compartment and/or targeting clones resistant to conventional treatments. Advances in single-cell genomic techniques and liquid biopsies from plasma and CSF, together with multiregional sampling of both primary and metastatic compartments, have the potential to fully capture the spectrum of intratumoral heterogeneity across the metastatic compartment. Repeat biopsies and sampling at the time of autopsy have the potential to significantly advance our knowledge of the biology of recurrent medulloblastoma. The next generation of preclinical modeling and clinical trials must take into account this clonal divergence. Additional clinical trials targeting genetic events present in the untreated primary tumor, but absent from the post-therapy metastases, are unlikely to confer benefit.

Quality of Life With Medulloblastoma

Neurocognitive adverse effects are common, and many survivors are incapable of living an independent life. Hearing loss is frequent in patients treated with radiation and/or platinum agents, and growth failure is nearly ubiquitous in prepubertal patients. Secondary malignancies, including secondary glioblastoma and leukemias, approach 3% to 5%. Studies of radiation avoidance in infants have shown that long-term functional outcomes are significantly better than in older irradiated children. Although advances in proton radiation may improve functional outcomes, there will likely be a limit to this improvement in the youngest children, and the risk of secondary malignancies is unlikely to decrease.

A major challenge in determining long-term functional outcomes has been a lack of long-term quality-of-life parameters in clinical trials. Recent studies have shown that the dose of both craniospinal irradiation and boost volume have a tremendous effect on neurocognitive outcome, which worsens over time. Reducing the boost volume to the tumor bed, as prescribed in the closed SJMB03 and ACNS0331 studies, and introducing proton radiotherapy have seemed to significantly improve neurocognitive outcomes, without compromising survival. Biologic parameters also seem to influence long-term neurocognitive outcome; patients with WNT and group 4 medulloblastoma seem to benefit most from reductions in craniospinal irradiation. Early interventions such as exercise, cognitive training, and possibly neuroprotectants, such as metformin (identifier: NCT02040376), have the potential to improve neurocognitive function in survivors.

Future Trial Design

Because the current large cooperative studies are either closed or nearing accrual it is of utmost importance that the next generation of clinical trials incorporate advances in biology. Currently stagnant survival rates will continue to exist if we continue to evaluate nonspecific therapies across biologically discrete groups; smaller studies evaluating more personalized approaches hold more promise for improving survival.

Although current studies are evaluating therapy de-escalation for patients with WNT tumors, more comprehensive and precise application of biologic risk stratification is needed to improve both survival and functional outcomes. A recent consensus on childhood medulloblastoma, in which patients are risk stratified by subgroup into very low risk, standard risk, high risk, and very high risk, provides a putative framework for the next generation of clinical trials. This risk stratification acknowledges MYC-amplified and/or metastatic group 3 and TP53-mutant SHH as being very high-risk diseases warranting novel upfront approaches. However, unless concepts from biologic studies, such as targeted therapies directed at metastatic disease in groups 3 and 4, are applied rationally, we are unlikely to see any discernable progress. As was the case with de-escalation trials in the 1980s, the adoption of molecular stratification confers an opportunity for bold studies that could potentially improve long-term quality of life and could diminish the risk of secondary malignancies while simultaneously maintaining or improving survival.

Disclosures provided by the authors are available with this article at jco.org.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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